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09/704,054	11/01/2000	Robert D'Amato	43170-249244	3798

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/704,054	D'AMATO, ROBERT	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,25-31 and 33-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,25-31 and 33-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 April 2007* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 23, 25-31 & 33-71 ARE PRESENTED FOR EXAMINATION

Applicant's amendment filed 4/19/2007 has been received and entered into the application. In light of the amendments, as well as the remarks of applicant at pages 13-16 of his amendment, the rejections of the claims under 35 U.S.C. § 102(b) as set forth in the previous Office action dated January 19, 2007 are hereby *withdrawn*.

Drawings

The replacement drawings were received on 4/19/2007. Said replacement drawings still include reference characters not mentioned in the description. Examiner suggests that applicant remove the reference characters from the drawings.

The drawings are objected to as failing to comply with 37 CFR § 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: the newly added designations of the structures (*e.g.* A, B, C, etc.) are not described in the specification. Corrected drawing sheets in compliance with 37 CFR § 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR § 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR § 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 25-31 and 33-71 are again rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an Enablement rejection.

Applicant's arguments have been fully considered but fail to persuade the Examiner of error in his determination that the claimed subject matter is not enabled by the disclosure. Firstly, Applicant has amended the claims to recite the treatment of tumors "associated with angiogenesis". However, Examiner is of the opinion that this claim limitation fails to limit the scope of the claimed subject matter. By their very nature, **all** "tumors" are associated with angiogenesis to some extent because in order to grow, a tumor **necessarily** requires vascularization. The Examiner is unaware of any tumor that can grow without blood vessels. Accordingly, Applicant's attempt to limit the subject matter of the claimed invention fails to persuade the Examiner that "tumors associated with angiogenesis" are distinct from "tumors" generally. Applicant next argues that sufficient guidance as to inhibiting growth, metastasis and recurrence of tumors associated with angiogenesis by administering an effective amount of thalidomide is provided in the specification. In support of this argument, Applicant directs the Examiner to page 7, lines 28-35; page 11, lines 9-20; and page 20, line 2 to page 23, line 2 of the

specification. The cited passages appear to be incorrect as none of the passages describes doses or formulations of thalidomide for the treatment of tumors. However, formulations are described at page 20, lines 22-34). Doses are described at page 21, lines 1-10. For oral administration the dose of thalidomide is taught to be in the range of 0.1 to 300 mg/kg/day, a 3,000-fold difference. It is noted that the formulations and administration routes taught in the specification are traditionally used for the administration of all therapeutic agents, regardless of the condition to be treated or the agent being administered. As such, the specification provides no specific guidance over that which is found throughout the prior art. The guidance provided with respect to dose and administration regimens was previously addressed by the Examiner in his analysis of the *Wands* factors (see previous Office Action, pages 10-11). Applicant concludes, based on the guidance provided by the specification, that all one of ordinary skill in the art has to do to practice the claimed invention is to "administer the specified amount of thalidomide using the specified routes of administration to the specified patients" (page 9 of Amendment). This, however, is simply not the case. The Examiner has provided overwhelming evidence to cast doubt on Applicant's assertion that simply administering thalidomide to a patient in the doses recited in the specification will result in the treatment of tumors (see pages 5-9 of previous Office Action). Thalidomide **has** been administered to patients to treat tumors in the doses and administration routes described in the instant specification and the treatment was **not** effective (see below).

Applicant next argues that the specification clearly describes that undesired angiogenesis occurs in certain tumors, and teaches the relationship between the inhibition of undesired angiogenesis and the inhibition of tumor growth (page 9 of Amendment). Examiner would like

to point out that this relationship has never been questioned. It is well known in the art that angiogenesis is associated with tumor growth. Based on this fact, Applicant's discovery that thalidomide inhibits angiogenesis led him to the present invention: administration of thalidomide to treat tumors associated with angiogenesis. However, as thoroughly discussed by the Examiner, the preponderance of the evidence suggests that the present invention does not work, *i.e.*, while thalidomide *does* inhibit angiogenesis in animal models of angiogenesis, its use in the treatment of tumors *in vivo* is unpredictable. While the model described by Applicant correlates with the inhibition of angiogenesis, it does not, *a priori*, correlate to the inhibition of tumor growth. The state of the art makes this abundantly clear (see below). While the art as a whole supports the idea that thalidomide *could* (theoretically) be used to treat tumors, the same art also demonstrates that such treatment is unpredictable and in most cases, completely ineffective. In fact, in the 14 years since the effective filing date of the instant application, Examiner has found no compelling literature that demonstrates that thalidomide is a safe, effective treatment for tumors.

Accordingly, the rejection of the claims as lacking enablement under 35 U.S.C. 112, 1st Paragraph is maintained for the reasons of record and reiterated below.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in

> question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) The breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

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[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to inhibiting the formation or growth of tumors associated with angiogenesis in humans comprising the administration of thalidomide. The relative skill of those in the art is high, generally that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Bach *et al.* (Acta Path., 1963, *59*:491-499) (cited by applicant), Gutman *et al.* (Anticancer Research, 1996, *16*:3673-3677), DiPaolo (Cancer Chemotherapy Reports, 1963, *29*:99-102) (cited by applicant), Thomas *et al.* (Current Opinion in Oncology, 2000, *12*:564-573) and Grabstald *et al.* (Clinical Pharmacology and Therapeutics, 1965, *6*:298-302) (cited by applicant). All references are cited for evidentiary purposes only.

Bach *et al.* studied the possible antineoplastic effect of thalidomide in experimental mouse models. The reference also discusses a report in which a woman with an X-ray resistant pelvic tumors was treated with thalidomide (400 mg daily). The tumors increased in size during the treatment. Bach *et al.* transplanted NJA tumors (a transplantable leukemia) and PBH tumors (an adenocarcinoma) in mice (page 494). The mice were then treated with varying doses (11.2, 112.0, 560.0 and 1120.0 mg/kg) of thalidomide (page 495). In mice with PBH tumors, all thalidomide treated mice died before controls (pages 496-497). In the NJA implanted mice, there was no significant effect of thalidomide on the survival times of the animals. Further, histological exam revealed no difference with regard to the extent of the leukemic infiltrations in the organs between treated and untreated mice (pages 496-497). The authors conclude that thalidomide had no antineoplastic effect (page 498).

Gutman *et al.* tested the efficacy of thalidomide in treating solid tumors in mice (Abstract). B16-F10 (melanoma) and CT-26 (colon carcinoma) cells were injected in mice and the mice then received 0.3-1.0 mg thalidomide (*id.*). There was no growth retardation in CT-26 bearing mice or in mice with pulmonary or peritoneal metastases of B16-F10 melanoma (*id.*). All tumors reached maximum size, similar to controls. Further, morphological exam revealed that in both thalidomide and control groups, all mice had developed an intact network of new blood vessels (*id.*). In conclusion, the authors report that the present study did not demonstrate a sustained, reproducible, anti-angiogenic effect of thalidomide in solid tumors growing in mice (page 3676).

DiPaolo also studied the effects of thalidomide in treating standard rat and mouse tumors, including adenocarcinoma, Ehrlich ascites, leukemia, sarcoma, Murphy-Sturm, lymphosarcoma and Walker 256 (Table 1). The daily dose of thalidomide was 500 mg/kg (*id.*). Based on the results of this study, DiPaolo concludes, "thalidomide is ineffective against transplantable cancers" (page 102).

Thus, in three separate studies, thalidomide was ineffective in inhibiting tumor growth in mouse models of cancer. Given this information, the skilled artisan would not expect thalidomide to be effective in treating tumors in humans.

Grabstald *et al.* is cited as evidence to support the unpredictability of treating tumors in humans using thalidomide. In fact, applicant admits that Grabstald *et al.* teach away from the present invention (see Response filed January 27, 2005). The reference teaches that thalidomide was administered to 71 patients with a wide spectrum of cancers (Abstract). There was no evidence of an objective response in any cancer except one patient with renal cell cancer (*id.* at

page 301). The authors conclude, "further random trials of this [thalidomide] drug against cancer in man are not indicated" (page 301).

Thomas *et al.* provides a review of the current role of thalidomide in cancer treatment. Although the article will not be discussed in detail, several points are pertinent to the present rejection. Firstly, the article states that the first oncology studies of thalidomide were reported in 1965 (Grabstald *et al.*, cited *supra*). Further, another study of 21 patients with various solid tumors who were treated with thalidomide revealed no tumor regressions (page 564). Secondly, several clinical trials of thalidomide have been carried out (pages 566-569). Thalidomide has shown moderate effects in some cancers (gliomas – 2/36 patients had partial response, 2/36 patients had a minor response, and 12/36 had stable disease; Kaposi's sarcoma – 6/17 patients had a partial response, 8/17 patients withdrew from toxicity; renal cell carcinoma – 3/18 patients had partial response) (pages 566-567). However, there were no objective tumor responses in 63 patients with metastatic prostate cancer, no objective responses in 17 patients with melanoma, no objective responses in 12 patients with breast cancer or 19 patients with ovarian carcinoma, and no objective tumor responses in 17 patients with metastatic squamous cell carcinoma of the head and neck (in fact, 94% of patients had progressive disease) (pages 567-568). Thirdly, a summary of FDA new drug applications issued for thalidomide between 1997 and 1998 yielded data on 480 patients treated for breast, CNS, prostate, skin, colon, pancreas and kidney malignancies. Thalidomide was given in doses up to 2400 mg daily. Responses were observed in 36 patients (7.5%), 10 of who had received combination therapy (*i.e.* not thalidomide alone), whereas 53% of patients discontinued therapy because of toxicity (page 568). Thus, it is clear that the

treatment of tumors in humans with thalidomide is extremely unpredictable and in the majority of cases completely ineffective.

Applicants own admissions provide further evidence that the treatment of tumors in humans with thalidomide is unpredictable. For example, in applicant's response filed 8/7/2006, applicant submitted that 19 references "indicate that thalidomide was not successful in inhibiting tumors in animals and humans" (page 16 of response filed 8/7/2006). Further, applicant states (emphasis added), "Moreover, Applicant respectfully points out that several references actually teach that **thalidomide has cancer-promoting or carcinogenic activity**" (*id.*). Further still, applicant states (emphasis added), "The references disclose **not only failure** but the **complete opposite effect** to the claimed invention" (*id.*). Applicant goes on to cite several studies wherein thalidomide was administered to humans with various tumors. Applicant concludes, "Again, all of these studies failed to provide any promise for thalidomide as effective in inhibiting the formation or growth of tumors in humans. The studies neither provide with any suggestion, **nor a reasonable expectation of success in inhibiting tumors in humans**" (*id.* at page 17). Thus, it is clear that thalidomide may actually promote cancer in some instances and in fact may have the opposite effect to that instantly claimed.

Thus, a preponderance of evidence suggests that treating tumors with thalidomide, particularly in humans, is extremely unpredictable and in most cases ineffective. Further, it is evident that thalidomide may actually have the complete opposite effect than those instantly.

2. The breadth of the claims

The claims vary in breadth; some (such as claim 23) vary broadly, reciting the treatment of any and all tumors associated with angiogenesis (both benign and cancerous) with

thalidomide. Others, such as claim 34, are narrower, reciting specific tumors. All, however, are extremely broad insofar as they disclose the general treatment of tumors with thalidomide.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat all of the various tumors claimed, particularly in humans. The working examples are limited to demonstrating the anti-angiogenic activity of thalidomide in animal models of angiogenesis. While angiogenesis is one factor involved in tumor growth, there are many other factors that influence tumor growth. As such, the fact that thalidomide inhibits angiogenesis does not reasonably suggest that it will be effective in inhibiting tumor growth. In fact, as discussed *supra*, the prior art supports the idea that thalidomide is ineffective in inhibiting tumor growth in humans. Thus, the applicant at best has provided specific direction or guidance only for the inhibition of angiogenesis with thalidomide. Although broad doses and administration routes of thalidomide are described in the specification, these doses and administration routes are contemplated to be useful for the treatment of any all angiogenic-related conditions. No reasonably specific guidance is provided concerning useful therapeutic protocols for any specific conditions or diseases, particularly the treatment of tumors.

Further, although many different conditions related to angiogenesis are contemplated to be treatable with thalidomide, Applicant has not provided any guidance on how one would specifically treat any particular disease or condition. Further still, there are no *in vitro* or *in vivo* experimental models of any diseases described, including cell proliferation or animal tumor

models. While the administration routes disclosed in the specification are standard routes of administration for therapeutic agents, applicant has provided no specific administration regimens (*e.g.* timing, specific doses, etc.) necessary to treat any specific tumor. Finally, while applicant recites a broad dose range (0.1 to 300 mg/kg/day), this dose range is not reasonably specific enough so as to provide adequate guidance to the skilled artisan in the treatment of tumors.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that thalidomide could be predictably used as a treatment for all tumors associated with angiogenesis as inferred in the claims and contemplated by the specification. A preponderance of the evidence suggests that thalidomide is ineffective in treating tumors in humans. Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference

claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23, 25-29, 31, 33-40, 58-62, 67-68 and 71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-46 of copending Application No. 11/096,155. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims and the claims of the '155 application recite the treatment of tumors comprising administering thalidomide. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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AU 1614

May 8, 2007

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER

5/8/07